

Amendments to the Claim:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Withdrawn) A crystal of a polypeptide comprising the Ig1-2-3 module of NCAM, said polypeptide comprising amino acid residues 1 to 289 of SEQ ID NO: 44, wherein said crystal comprises atoms arranged in a spatial relationship represented by the structure co-ordinates of Table 2 (Figure 2) or by coordinates having a root mean square deviation therefrom of not more than 2.5 Å.

2. (Withdrawn) The crystal according to claim 1, wherein the polypeptide consists of amino acid residues 1 to 289 of SEQ ID NO: 44 and an extra amino acid sequence of 1 to 4 amino acids residues.

3. (Withdrawn) The crystal according to claim 1, wherein said crystal diffracts X-rays for determination of atomic co-ordinates to a resolution of at least 4 Å.

4. (Withdrawn) The crystal according to claim 1, wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates to a resolution at most 5. 0 Å.

5. (Withdrawn) The crystal according to claim 4, wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates to a resolution 1.5Å

6. (Withdrawn) The crystal according to claim 1, wherein said crystal has unit cell dimensions of  $a=51.5$  Å,  $b=108.5$  Å,  $c= 149.0$  Å,  $\alpha=90^\circ$ ,  $\beta=90^\circ$ ,  $\gamma=90^\circ$ .

7. (Withdrawn) A method for selecting a candidate compound capable of modulating differentiation, adhesion and/or survival of NCAM presenting cells by modulating the interaction of

i) the Ig1 module of one individual NCAM molecule with

the Ig3 module of another individual NCAM molecule, and/or

ii) the Ig2 module of one individual NCAM molecule with the Ig3 module of another individual NCAM molecule, and/or

iii) the Ig2 module of one individual NCAM molecule with the Ig2 module of another individual NCAM molecule, said method comprising the steps of

- providing a crystalline polypeptide according to claim 1,
- generating a structural model of the Ig1-2-3 module of NCAM of (a) by using the computer modelling techniques;
- in-silico evaluating compounds for the capability of

i) binding to the Ig1 module of NCAM at the NCAM homophytic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking and/or modulating the interaction between the Ig1 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

ii) binding to the Ig3 module of NCAM at the NCAM homophytic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig1 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iii) binding to the Ig2 module of NCAM at the NCAM homophytic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking the interaction between Ig2 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iv) binding to the Ig3 module of NCAM at the NCAM homophytic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking and/or modulating the binding between the Ig3 and Ig2 modules of NCAM, wherein said

modules are from two individual NCAM molecules, and/or

v) binding to the Ig2 module of NCAM at the NCAM homophylic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking and/or modulating the interaction between the Ig2 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules, by using the structural model of the Ig1-2-3 module of NCAM of (b);

- d) selecting a candidate compound capable of at least one interaction of (c), and
- e) testing the candidate compound of (d) in an *in vitro* assay for the capability of modulating differentiation, adhesion and/or survival of NCAM presenting cells, said assays comprising at least one NCAM presenting cell, and /or
- f) testing the candidate compound of (d) in an assay comprising evaluating the capability of the compound of at least one interaction of (b) by contacting the compound with at least one individual fragment of an NCAM molecule, said fragment comprising a sequence of consecutive amino acid residues corresponding to the sequence of the Ig1-2-3 module of NCAM comprising residues 1 to 289 of the sequence set forth in SEQ ID NO: 44.

8. (Currently Amended) A compound capable of binding to the neural cell adhesion molecule (NCAM) homophylic binding site composed of the Ig1, Ig2 and Ig3 modules, wherein said compound is capable of

i) binding to the Ig1 module of NCAM at said NCAM homophylic binding site, and thereby mimicking and/or modulating the interaction between the Ig1 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM

molecules of opposing contacting cells, and/or

ii) binding to the Ig3 module of NCAM at said NCAM homophylic binding site, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig1 modules of NCAM, wherein said modules are from two individual NCAM molecules of opposing contacting cells, and/or

iii) binding to the Ig2 module of NCAM at said NCAM homophylic binding site, and thereby mimicking the interaction between Ig2 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules of opposing contacting cells, and/or

iv) binding to the Ig3 module of NCAM at said NCAM homophylic binding site, and thereby mimicking and/or modulating the binding between the Ig3 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules of opposing contacting cells, and/or

v) binding to the Ig2 module of NCAM at said NCAM homophylic binding site, and thereby mimicking and/or modulating the interaction between the Ig2 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules of opposing contacting cells,

said compound being

(I) (a) a peptide sequence identified as SEQ ID NO: 1, 2, 3, 4, 7, 10, 11, 12, 13, 14, 16, 17, 18, 40 or 41, ~~or being a fragment or a variant of said sequence, wherein said peptide sequence is selected by the method according to claim 20~~

(b) a peptide which is a fragment of (a), consisting of at least 5 amino acids,

(c) a peptide consisting of a peptide sequence according to (a) and up to 10 additional amino acids,

(d) a peptide which differs from (a), (b) or (c) solely by one or more amino acid substitutions, but comprises at least a five amino acid fragment of a peptide of (a) or comprises a sequence at least 50% identical to a peptide of

(a), or

(II) an oligomer or polymer comprising a plurality of peptides according to (I) above, which oligomer or polymer either consists of a plurality of peptides according to (I) above, or comprises a non-NCAM carrier moiety to which said peptides are attached.

9. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence WFSPNGEKLSPNQ (SEQ ID NO: 1).

10. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence YKCVVTAEDGTQSE (SEQ ID NO: 2).

11. (Cancelled).

12. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence QIRGIKKTD (SEQ ID NO: 4).

13. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence DVR (SEQ ID NO: 5).

14. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence RGIKKTD (SEQ ID NO: 6).

15. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence DVRRGIKKTD (SEQ ID NO: 7).

16. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence KEGED (SEQ ID NO: 8).

17. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence IRGIKKTD (SEQ ID NO: 9).

18. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence KEGEDGIRGIKKTD (SEQ ID NO: 10).

19. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence DKNDE (SEQ ID NO: 11).

20. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence TVQARNNSIVNAT (SEQ ID NO: 12).

21. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence SIHLKVFVAK (SEQ ID NO: 13).

22. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence LSNNYLYQIR (SEQ ID NO: 14).

23. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence RFIVLSNNYQI (SEQ ID NO: 15).

24. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence KKDVRFIVLSNNYQI (SEQ ID NO: 16).

25. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence QEFKEGEDAVIV (SEQ ID NO: 17).

26. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence KEGEDAVIVCD (SEQ ID NO: 18).

27. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence AFSPNNGEKLSPNQ (SEQ ID NO: 40).

28. (Currently Amended) The compound according to claim 8, said compound having consisting of the amino acid sequence AKSVVTAEDGTQSE (SEQ ID NO: 41).

29. (Cancelled)

30. (Withdrawn) The method of claim 42, wherein the medicament is for treating normal, degenerated or damaged NCAM presenting cells.

31. (Withdrawn) The method of claim 42, wherein the medicament is for treatment comprising the stimulation of differentiation and/or survival of NCAM presenting cells.

32. (Withdrawn) The method of claim 42, wherein the medicament is for treating the diseases and conditions of the central and peripheral nervous system, or of the muscles or of various organs.

33. (Withdrawn) The method of claim 42, wherein the medicament is for treating the diseases or conditions of the central and peripheral nervous system, such as postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression; for treatment of diseases or conditions of the muscles including conditions with impaired function of neuro-muscular connections, such as after organ transplantation, or such as genetic or traumatic atrophic muscle disorders; or for treatment of diseases or conditions of various organs, such as degenerative conditions of the gonads, of the pancreas such as diabetes mellitus type I and II, of the kidney such as nephrosis and of the heart, liver and bowel.

34. (Withdrawn) The method of claim 42, wherein the medicament is for treating the postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood

disorders, such as manic depression.

35. (Withdrawn) The method of claim 42, wherein the medicament is for promoting the wound-healing.

36. (Withdrawn) The method of claim 42, wherein the medicament is for treating the cancer.

37. (Withdrawn) The method of claim 42, wherein the medicament is for preventing the cell death of heart muscle cells, such as after acute myocardial infarction, or after angiogenesis.

38. (Withdrawn) The method of claim 42, wherein the medicament is for promoting the revascularisation.

39. (Withdrawn) The method of claim 42, wherein the medicament is for stimulating the ability to learn and/or of the short and/or long-term memory.

40. (Cancelled)

41. (Previously Presented) A pharmaceutical composition comprising one or more compounds as defined in claim 8.

42. (Withdrawn) A method of treating a disease wherein modulating differentiation, adhesion and/or survival of NCAM presenting cells is essential for the treatment, which comprises administering to a subject in need thereof a therapeutically effective amount of a medicament comprising a compound according to claim 8.

43. (Withdrawn) A method of in-silico screening of a candidate compound for its ability to modulate NCAM homophylic adhesion-dependent neural plasticity, cell differentiation and/or survival, which comprises contacting said candidate compound with a crystal according to claim 1 and observing the interaction of said compound with said crystal.

44. (New) The compound according to claim 8, wherein said peptide sequence is selected by a method comprising the steps of

- a) providing a crystalline polypeptide according to claim 1,

- b) generating a structural model of the Ig1-2-3 module of NCAM of (a) by using the computer modelling techniques;
- c) in-silico evaluating compounds for the capability of
  - i) binding to the Ig1 module of NCAM at the NCAM homophytic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking and/or modulating the interaction between the Ig1 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or
  - ii) binding to the Ig3 module of NCAM at the NCAM homophytic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig1 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or
  - iii) binding to the Ig2 module of NCAM at the NCAM homophytic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking the interaction between Ig2 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or
  - iv) binding to the Ig3 module of NCAM at the NCAM homophytic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking and/or modulating the binding between the Ig3 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or
  - v) binding to the Ig2 module of NCAM at the NCAM homophytic binding site composed of the Ig1, Ig2 and Ig3 modules, and thereby mimicking and/or modulating the interaction between the Ig2 and Ig2 modules of NCAM, wherein said modules are from two individual

NCAM molecules,  
by using the structural model of the Ig1-2-3 module of NCAM of (b);

- d) selecting a candidate compound capable of at least one interaction of (c), and
- e) testing the candidate compound of (d) in an in vitro assay for the capability of modulating differentiation, adhesion and/or survival of NCAM presenting cells, said assays comprising at least one NCAM presenting cell, and /or testing the candidate compound of (d) in an assay comprising evaluating the capability of the compound of at least one interaction of (b) by contacting the compound with at least one individual fragment of an NCAM molecule, said fragment comprising a sequence of consecutive amino acid residues corresponding to the sequence of the Ig1-2-3 module of NCAM comprising residues 1 to 289 of the sequence set forth in SEQ ID NO: 44.

45. (New) The compound according to claim 8 wherein the carrier of (II) is a lysine dendrimer backbone.

46. (New) The compound according to claim 8 wherein the carrier of (II) is a protein.

47. (New) The compound according to claim 46 wherein the carrier of (II) is bovine serum albumin.

48. (New) The compound according to claim 8 wherein the carrier of (II) is a lipophilic dendrimer, a micelle-like carrier formed by lipophilic derivatives, a starburst carbon chain polymer conjugate, or a ligand presenting assembly based on a derivative of diethylaminomethane.

49. (New) The compound according to claim 8 wherein (I) applies.

50. (New) The compound of claim 49 wherein the peptide of (I) (d) comprises a sequence at least 85% identical to a peptide of (I) (a).

51. (New) The compound of claim 49 wherein the peptide of (I) (d) comprises a sequence differing from a peptide of (I) (a) solely by a single substitution.

52. (New) The compound of claim 49 wherein the peptide of (I) (d) comprises a sequence which differs from a peptide of (I) (a) solely by one or more conservative substitutions, such being defined as

(1) replacement of an amino acid selected from the group consisting of Gly, Ala, Val, Leu and Ile with another amino acid of the same group,

(2) replacement of an amino acid selected from group consisting of Asp, Glu, Asn and Gln with another amino acid of the same group,

(3) replacement of an amino acid selected from the group consisting of Phe, Tyr, Trp, His, and Pro with another amino acid of the same group,

(4) replacement of an amino acid selected from the group consisting of Arg, Lys and His with another amino acid of the same group,

(5) replacement of Cys with an amino acid selected from the group consisting of Asp, Glu, Lys, Arg, His, Asn, Gln, Ser, Thr and Tyr,

(6) replacement of an amino acid selected from the group consisting of Pro, Ala, Gly, Ser and Tyr with another amino acid of the same group, and

(7) replacement of an amino acid selected from the group consisting of Leu, Ile, Val and Met with another amino acid of the same group.

53. (New) The composition of claim 52 wherein the peptide of (I) (c) comprises a sequence differing from a peptide of (I) (a) solely by a single conservative substitution.

54. (New) The compound of claim 49 wherein said fragment of (I) (b) differs from a peptide of (I) (a) by deletion of not

more than 8 amino acids.

55. (New) The compound of claim 49 wherein said fragment of (I)(b) differs from a peptide of (I)(a) by deletion of not more than 6 amino acids.

56. (New) The compound of claim 49 wherein said fragment of (I)(b) differs from a peptide of (I)(a) by deletion of not more than 4 amino acids.

57. (New) The compound of claim 49 wherein said fragment of (I)(b) differs from a peptide of (I)(a) by deletion of not more than 2 amino acids.

58. (New) The compound of claim 49 that is a peptide of (I)(a) or (I)(b).

59. (New) The compound of claim 49 that is a peptide of (I)(a).

60. (New) The compound of claim 45 wherein said oligomer or polymer of (II) comprises at least two identical peptides according to (I).

61. (New) The compound of claim 45 wherein said oligomer or polymer of (II) comprises at least four identical peptides according to (I).

62. (New) The compound of claim 61 wherein the carrier is a lysine dendrimer backbone or bovine serum albumin.

63. (New) The compound of claim 62 wherein the fragment of I(b) differs from a peptide of (I)(a) by deletion of not more than 2 amino acids, and the peptide of (I)(d) is at least 85% identical to a peptide of (I)(a).

64. (New) The compound of claim 49 that is a peptide of (I)(a), (I)(b) or (I)(c).

65. (New) The compound of claim 49 that is a peptide of (I)(a) or (I)(c).